IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

CHEN-MING HSIAO *et al.*

Serial No.:	10/608,073	Examiner:	*to be assigned*
Filed:	30 June 2003	Art Unit:	*to be assigned*

For: THE KMST ISOEUGENOL DERIVATIVES AND PHARMACEUTICAL ACTIVITY

INFORMATION DISCLOSURE STATEMENT

Mail Stop :
Commissioner for Patents
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Alexandria, VA 22313-1450

Sir:

In accordance with 37 C.F.R. §1.56, and §§1.97 and 1.98 as amended, Applicant cites, describes and provides copies of the following art references:

References

1. Altavilla *et al.*, "*The Lazaroid, U-74389G, inhibits inducible nitric oxide synthase activity, reverses vascular failure and protects against endotoxin shock,*"European Journal of Pharmacology, Vol. 369, pp. 49-55, 1999.
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Discussion

Altavilla discloses that lipopolysaccharide adminitration reduced survival rate in a rat model of endotoxin shock.

Aubriot et al. and Yeun-Chih Huang et al. disclose that aryloxypropanolamines and especially those which are isoeugenol-based ones have anti-oxidizing activities, in addition to their ß-adrenoceptor blocking effects

In Dunn et al. And Koyama et al., the ability of α_2-adrenoceptor blocking antidepressant treatment to attenuate LPS-induced-depression in rats is cited as evidence that inflammatory cytokines play an important role in depression

In Cohen et al. and Owens et al., trazodone with 5-HT agonist/antagonist activity, 5-HT

reuptake inhibition and adrenoceptor blocking activities is taken as a reference to evaluate associated pharmacologic activities.

Corrêa et al. and Díaz-Cabiale et al. disclose that central administration of yohimbine increases BP and HR.

Curro et al. investigates the mechanism by which serotoinin causes contraction of canine venous smooth muscle.

Dobrucki et al. and Tseng et al. disclose that the action of clonidine is dependent on activation of eNOS and the action of LPS is dependent on activation of iNOS.

In Duan et al., intra-cisternal injections of KMST, yohimbine, and clonidine were performed in rats.

Duka et al. and MacMillan et al. disclose that the α_{2A}-adrenergic subtype is located in the CNS and is concentrated in the cardiovascular control center of the brainstem, and α_{2B}-adrenergic receptors are located in arterial vascular smooth muscle cells and cause peripheral vasoconstriction.

Elenkov et al. and Hasko et al. disclose that the non-selective β-adrenoceptor blocker propranolol prevents the effects of α_2-adrenoceptor blockade on TNF-α plasma levels induced by

LPS and associated cytokine formation in mice.

Fujimoto et al. discloses that α_{2B}-adrenoceptor agonist activity of clonidine in thoracic aorta produces contractile activity.

Girard et al. and Ulker et al. disclose that iNOS inhibitors and antioxidants reduce LPS-induced vascular hyporesponsiveness.

Glaser et al. and Spengler et al. disclose that both noradrenaline and α_2-adrenergic agonists augment LPS-induced TNF production, and that this augmentation was prevented by the α_2-adrenergic antagonist yohimbine.

Haddjeri et al. discloses that some ß-adrenoceptor blockers, such as pindolol, have been found to have nanomolar binding affinities for 5-HT_{1A} receptors and have prevented some 5-HT_{1A} receptor-mediated responses.

Hasko et al. and Hirata et al. disclose that α_2-adrenoceptor blockers may provide some protection in rats against bacterial lipopolysaccharide (LPS)-induced hyperglycemia, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), corticosteroid release, and mortality.

Hatanaka et al. and Helmeste et al. disclose the method for measuring inhibition of 5-HT

reuptake.

Yu-Chen Huang et al. discloses the inhibitory effect of DCDC on lipopolysaccharide-induced nitric oxide synthesis in RAW 264.7 cells.

Ko et al. and Pitzalis et al. disclose that ß-adrenergic blocking agents with serotonergic properties have proved beneficial to depressed patients, notably those with myocardial infarction and congestive heart failure.

Krege et al. discloses that trazodone has higher affinity for human α_1-adrenoceptors than for α_2-adrenoceptors, but did not discriminate between subtypes of human α_1-, α_2-adrenoceptors.

Kubo et al. discloses that injection of the selective α_2 antagonist yohimbine into the NTS produces hypertension and tachycardia.

Lin et al. discloses that intravenous LPS produces a biphasic reduction in BP in anesthetized rats.

Llado et al. discloses that some selective or subtype-selective α_2-adrenoaceptor blockers such as yohimbine, rauwolscine, and phentolamine possess affinity for 5-HT_{1A} receptors in the rat brain.

Loegering et al. discloses that antioxidants can ameliorate depression of vascular reactivity caused by LPS.

Maitra et al. discloses that hypoglycemia in severe septic conditions occurs because the rate of glucose use exceeds the rate of production.

Molina-Holgado et al. and Lavicky disclose that stimulation by increased plasma catecholamines during early sepsis may cause sympathetic activation of the CVS.

Murphy et al. discloses three subtypes of α_2-adrenoceptors, designated as α_{2A}, α_{2B} and α_{2C}.

Nickola et al. discloses that a reciprocally permissive interaction occurs between TNF-α and α-adrenoceptor activation and that changes in pre-synaptic adrenergic sensitivity, as well as in neuronal sensitivity to TNF-α have been implicated in the action of anti-depressant drugs.

Shen et al. discloses that lipopolysaccharide (LPS)-induced inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1) and interferon (IFN) can be regulated by blocking α_2-adrenergic receptors, which are involved in the balance between noradrenergic and serotonergic systems in central neurons.

Smith et al. suggests that both 5-HT_{2A} and 5-HT_{1B} receptors are involved in vascular

contraction.

Sugita et al. discloses that aminoguanidine inhibits LPS-induced hyperglycemia by decreasing glycogenolysis and gluconeogenesis.

Szabo et al. discloses that many pathobiochemical alterations occur in endotoxic shock: a dramatic increase in eicosanoid and platelet activation factor production, cytokine release (in particular IL and TNF-α, activation of the L-arginine-nitric oxide (NO) pathway, formation of oxygen-centered free radicals and activation of the plasmatic coagulation cascade, fibrinolysis and complement pathway.

Szelenyi et al. discloses that *in vivo*, α_2- and ß-adrenoceptors on macrophages can be activated by the endogenous ligand noradrenaline, released from noradrenergic varicosities and by adrenergic drugs.

Tsuchiya et al. discloses the method for determining the scavenging ability of the test compounds on aqueous peroxyl radicals.

Urban et al. discloses that clonidine-like drugs owe part of their bradycardic effect to activation of peripheral cardiac pre-synaptic α2-autoreceptors.

Roux et al. discloses that 5-HT_{2A} receptors mediate the contractile response of blood vessels.

Neuten et al. discloses that ketanserin is a potent antagonist of the vasoconstrictor effects of 5-hydroxytryptamine.

Victor et al. discloses that ascorbic acid affects macrophage activity in mice during endotoxic shock and that the toxic effects of oxygen radicals produced by immune cells can be controlled to certain degree by endogenous anti-oxidants.

Villalobos-Molina discloses that noradrenaline neurons modulate the activity of the 5-HT(serotonin, 5-Hydroxytryptamine) system and that several lines of evidence support the theory that the 5-HT system influences brain noradrenaline neurons.

Lang discloses that, under septic conditions, non-selective β-adrenoceptor blocker propranolol prevents an increase in glucose production.

Lane et al. discloses that microinjection of fluoxetine into the NTS increases BP and HR.

Wu et al. (2001) disclose a method of an isolation of thoracic aorta.

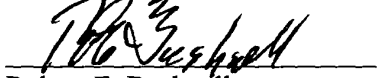
Wu et al. (2002) discloses that reactive oxygen species, superoxides in particular, have been implicated in the potentiation of iNOS induction in cells.

Yeh discloses that rats are anaesthetized with pentobarbital sodium and mounted in a David-Kopf stereotaxic instrument for intra-cisternal injections.

The citation of the foregoing references is not intended to constitute an assertion that other or more relevant art does not exist. Accordingly, the Examiner is requested to make a wide-ranging and thorough search of the relevant art.

No fee is incurred by this Statement.

Respectfully submitted,



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